Biocomputing and Drug Design

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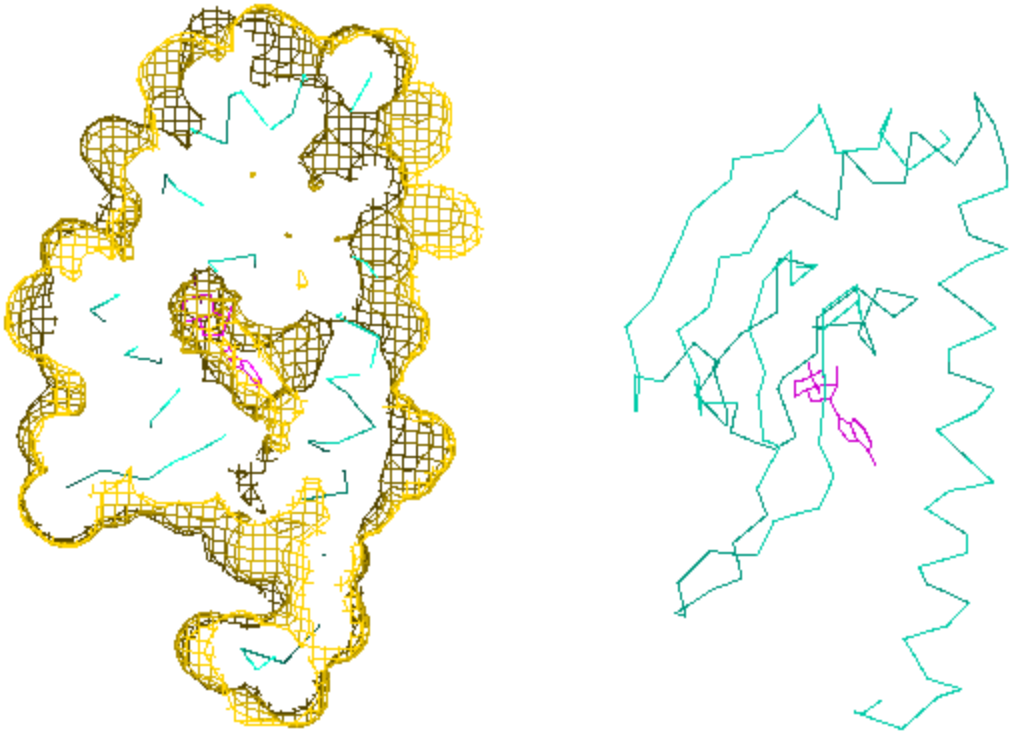
Proteins as Cellular Targets of Medical Drugs

The cellular targets (or receptors) of many drugs used for medical treatment are proteins. By binding to the receptor, drugs either enhance or inhibit its activity. Basically there are two major groups of receptor proteins: proteins that "float" around in the cytoplasm of the cell, and proteins that are incorporated into the cell membrane. In the latter case, a drug does not even need to enter the cell, it can bind simply to an extracellular binding site of the protein and control intracellular reactions from the outside.



Two representations of a drug or "ligand" which is bound to a specific region ("domain") of a "receptor" protein. The first image shows caves and cavities of the binding domain (visualised by the yellow grid). The ligand is shown in purple. It is buried in an internal cave of the protein. The second image displays the folding pattern of the protein and shows the structural organisation of the binding site. The protein backbone is drawn in blue, the ligand in purple.

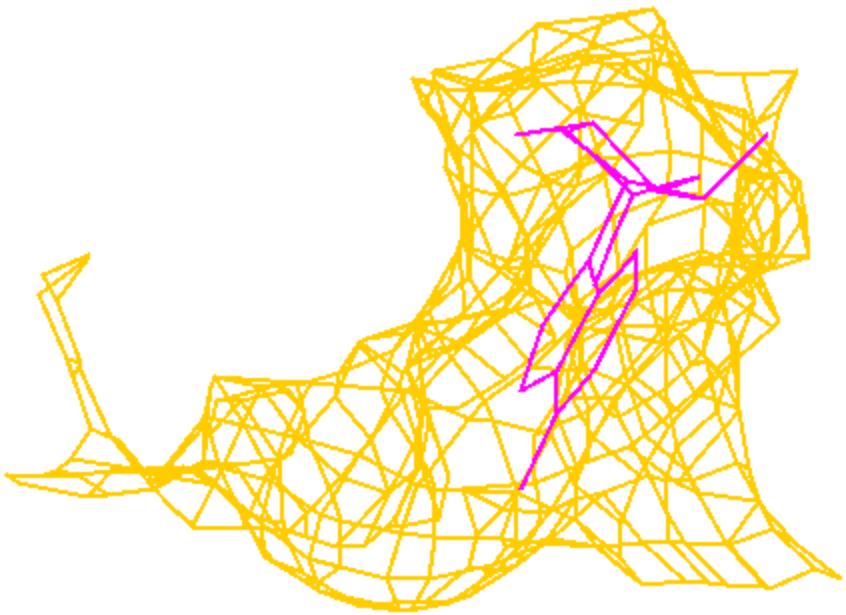
Drug Specificity and Side Effects

An important criterion to determine the medical value of a drug is specificity: the physiological effect of the drug should be as clearly defined as possible. It has to specifically bind to the target protein in order to minimise undesired side-effects. The idea that molecules can interact in a highly specific manner has a long history in medical chemistry. A century ago, Fischer and Ehrlich already used a "lock-and-key" analogy.

Undesired side-effects, however, are not always an indication for insufficient specificity of drugs as these effects might also result from a reaction of our body to the desired and therefore successful regulation of the malfunctioning biochemical process.

The Molecular Basis of Drug Specificity

On the molecular level specificity includes two more or less independent mechanisms: first the drug has to bind to its receptor site with a suitable affinity (better binding means lower doses) and second it has to either stimulate or inhibit certain movements of the receptor protein in order to regulate its activity. Both mechanisms are mediated by a variety of interactions between the drug and its receptor site. Usually tens of thousands of compounds have to be screened to find a promising new drug and only very few of these candidates will make their way through the final clinical tests. Looking for help from powerful computers seems straightforward. So how can they help?



A more detailed image of the ligand binding cavity shown in the beginning. Again, the ligand is displayed in purple, and the yellow grid shows the contour of the protein at the binding site.

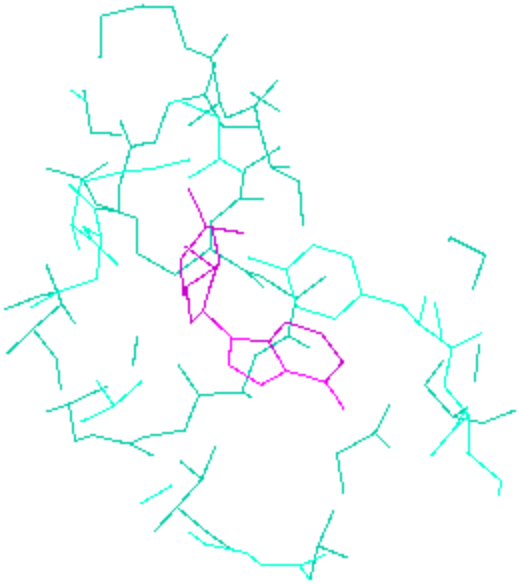
"Rational" Drug Design

The input of biocomputing in drug discovery is twofold: firstly the computer may help to optimise the pharmacological profile of existing drugs by guiding the synthesis of new and "better" compounds. Secondly, as more and more structural information on possible protein targets and their biochemical role in the cell becomes available, completely new therapeutic concepts can be developed. The computer helps in both steps: to find out about possible biological functions of a protein by comparing its amino acid sequence to databases of proteins with known function, and to understand the molecular workings of a given protein structure. Understanding the biological or biochemical mechanism of a disease then often

suggests the types of molecules needed for new drugs.

Techniques Applied

In all cases, the aim of using the computer for drug design is to analyse the interactions between the drug and its receptor site and to "design" molecules that give an optimal fit. The central assumption is that a good fit results from structural and chemical complementarity to the target receptor. The techniques provided by computational methods include computer graphics for visualisation and the methodology of theoretical chemistry. By means of quantum mechanics the structure of small molecules can be predicted to experimental accuracy. Statistical mechanics permits molecular motion and solvent effects to be incorporated. Basically statistical mechanics is a three-dimensional equivalent of describing the position of billiard balls using Newton's law of motion.



The ligand (purple) is shown together with possible interaction partners of the binding site (blue). Residues within 10 Angstrom (10^{-10} meters) of the ligand are considered as putative interaction partners.

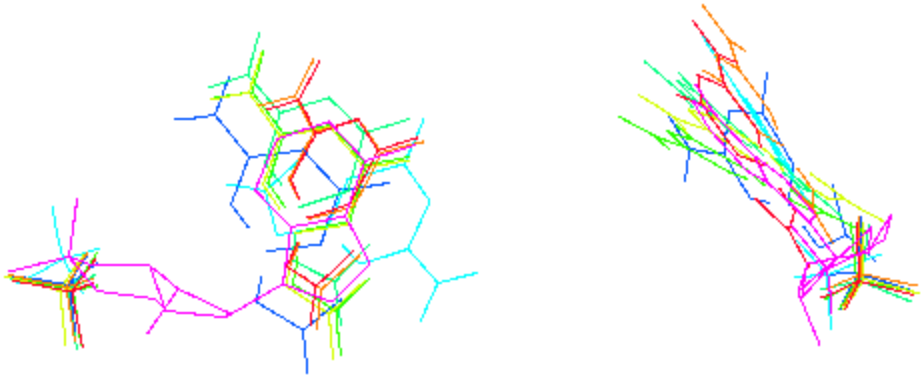
Drug Design Using Known Receptor Structures

The best possible starting point is an X-ray crystal structure of the target site. If the molecular model of the binding site is precise enough, one can apply docking algorithms that simulate the binding of drugs to the respective receptor site. In a first step these programs create a negative image of the target site, as shown above, place the putative ligands into the site, as shown down below , and finally they evaluate the quality of the fit.

What if we don't Know the Structure of the Receptor ?

Even if the structure of the receptor site is unknown the computer may help to figure out how it might look by comparing the chemical and physical properties of drugs that are known to act at a specific site. Moreover, if the amino acid sequence of the receptor site is known, one can try to predict the structure of the unknown site. This can either be done

"from scratch" (which still is rather an adventure...) or by using a known structure of a related protein as template. If about 25 to 30 % of the amino acid residues are identical in two proteins, one may assume, that the three-dimensional structure of these two proteins is very similar, see also Joelle Thonnard's contribution. The technique used for this approach is called "homology modelling": the folding pattern of the template protein is maintained and the side chain atoms of the template protein are replaced by the side chain atoms of the unknown protein. Basically, the three-dimensional structure of a protein is represented by the three-dimensional organisation of the backbone atoms. The side chain atoms, which are different for all 20 amino acids, define the specific interactions with ligands or other protein domains. Replacing the side chains while maintaining the backbone therefore allows to keep the general structure of the protein and to evaluate the specific properties of the unknown protein with respect to ligand interactions.



These two images show possible orientations and conformations of the ligand in the binding pocket (same as above) in side view (first image) and top view (second image). The different conformations are generated and evaluated using computer programs. Similar calculations are performed for a set of different molecules. Those molecules giving the highest interaction energies are considered for further experimental tests. The calculations were done using FlexX.

Future Perspectives

During the last years, we have witnessed a huge progress in the development of new methods in the field of molecular biology and computer science. This has improved the tools for rational drug design significantly. More and more new drugs are developed with the help of computer techniques. A prominent example is the design of potent HIV protease inhibitors (Science, 263, 1994, 380). The design was based on knowledge of the target structure.
The computational power is yet insufficient to simulate complex biochemical reactions or even to monitor conformational changes of proteins caused by the binding of ligands. There are, however, examples where the opposite process, the unbinding of a ligand, was monitored (Science, 271, 1996, 997). These results confirm that we are able to successfully simulate and predict the basic principles of ligand-receptor interactions.

All figures were prepared using the WHATIF software package.

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